REMARKS

Claims 1-7, 9-10, 12, 14, 16-21, 23-26, 28-34, 44-49, 51-52, 54-60, 62-63, 65-66, 68-75 and 129-140 are presented for examination.

Claims 8, 11, 13, 15, 22, 27, 35-43, 50, 53, 61, 64, 67 and 76-128 are canceled without disclaimer or prejudice. New Claims 135-140 are added. The new claims are supported at least by paragraph [0021] of the published application.

No new matter has been added, and entry is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Office Action rejected Claims 1-6, 9-10, 12, 14, 18-21, 23-26, 28-33, 45-49, 51-52, 54-59, 62-63, 65-66, and 69-75 as being unpatentable over U.S. 5,814,014 (Elsberry *et al.*) in view of U.S. 5,433,946 (Allen *et al.*), U.S. 2003/0129186 (Beliveau *et al.*), U.S. 5,911,969 (Axworthy *et al*), and Crystallographic analysis of the pH-dependent binding of iminobiotin by streptavidin," Protein Sci., 1997; 6(6):1338-1342 ("Athappilly *et al.*"). However, the *prima facie* case of obviousness has not been established because Athappilly *et al.* fails to teach or suggest a *streptavidin-biotin* complex linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH. Further, the cited references fail to teach delivery to the central nervous system (CNS) wherein the system provides for enhanced transcytosis of *therapeutic* proteins into cells as recited in new Claims 135-137.

Presently pending Claim 1 recites that the linker is a *streptavidin-biotin* complex linking the protein with the transport aid in a pH-dependent manner. Although the Office Action alleged Athappilly *et al.* teaches that the "therapeutic protein and transport aid remain operably linked in

a neutral pH environment and that the therapeutic protein disassociates at an acidic pH" (page 9 of Action citing Abstract), this allegation is incorrect because the reference teaches away from a *streptavidin-biotin* complex and fails to contemplate therapeutic use. Instead, Athappilly *et al.* teaches that "Core streptavidin (Paler et al., 1987) binds **biotin** very tightly" where "Variations in pH **do not** influence this binding," and that the use is limited to purification in affinity chromatography. *See* Athappilly *et al.* at p. 1341, col. 1. Hence, Athappilly *et al.* teaches the opposite conclusion with respect to the *streptavidin-biotin* complex of Claim 1. This teaching does not necessarily conflict with the claimed invention because as a preliminary matter, one of ordinary skill in the art would not understand from Athappilly *et al.* that disassociation of the therapeutic protein and transport aid would occur at low pH values wherever in the body those might occur, especially since Athappilly *et al.* is directed to affinity chromatography and not to *in vivo* treatment of a human patient. Nonetheless, Athappilly *et al.* clearly teaches away from use of the presently claimed *streptavidin-biotin* complex in a pH dependent manner.

Delivery to the central nervous system (CNS) wherein the claimed system of Claim 1 provides for enhanced transcytosis of therapeutic proteins into cells is wholly different from the purifying step contemplated by the reference with respect to affinity chromatography. Although the Office Action alleged Athappilly *et al.* teaches that the pH dependent affinity of streptavidin/avidin and *2'iminobiotin* is a characteristic that "does not exist solely within the confines of crystallographic analysis or affinity chromatography" but is inherent in the chemical structure of the compounds, the differences in design and purpose of crystallographic analysis or affinity chromatography makes its application for *in vivo* use in drug delivery across the blood brain barrier unexpected. This is because known uses of affinity chromatography include antibody affinity, immobilized metal ion affinity chromatography and purification of

recombinant proteins with purification being the primary objective. In contrast, the claimed invention is directed to a therapeutic use such that the therapeutic protein and transport aid remain operably linked at a neutral pH environment of the CSF, but become dissociated once taken up by cells into lysosomal compartments, or other acidic intracellular organelles. Moreover, in order to achieve the desired result, the claimed system requires that the proteins be first modified by conjugation to a "transport aid that facilitates the cellular uptake of said therapeutic protein," where selective release via pH dependency only occurs after the conjugates are transported across the blood-brain barrier. Hence, pH dependency can be used to mechanistically sense when the conjugate has reached the target lysosomal compartments, or other acidic intracellular organelles. In contrast, affinity chromatography merely uses binding to a substrate of some type to bind a target for purification. There is a clear difference between affinity chromatography in a laboratory setting and the presently claimed modification of a protein formulation to allow for enhanced uptake of therapeutic proteins by cells of the central nervous system *in vivo*. Hence, it is respectfully submitted that the Office Action erred in its evaluation of the differences between the claimed invention and the prior art.

Regarding Claims 130, 132, and 134, there is no teaching in Athappilly *et al.* of use of the complex in cerebral spinal fluid or in lysosomal departments of the patient. Therefore, the Office Action erred in its valuation of the differences between the claimed invention and the prior art.

Beliveau *et al.* teaches that a streptavidin-biotin complex can be used as a label, which can be optionally attached to a component for radio-labeling. However, Beliveau *et al.* does not teach that the streptavidin-biotin complex can be used for any purpose other than for marking or labeling or that the streptavidin-biotin complex itself can be used to link a therapeutic protein

and a transport aid together. In fact, Beliveau *et al.* expressly teaches at paragraph [0187] that the linker is not a critical aspect of the invention. The Office Action alleged that this argument does not address the "linker" as being a non-critical aspect of the invention. However, the Office Action asserts that the compound defined as a "label" of Beliveau *et al.* is the "linker" at issue. Despite the varied labels given to the streptavidin-biotin complex of Beliveau *et al.*, Beliveau *et al.* explicitly teaches that this complex is a non-critical aspect of the invention at paragraph [0187].

The Office Action alleged that the use of streptavidin-biotin as a linker in conjugating proteins is well known in the art, as evidenced by Axworthy *et al.* and Athappilly *et al.* However, Axworthy *et al.* merely teaches streptavidin-antibody conjugates or biotinylated cytokines. If such linker is "well known," the cited references do not support such an allegation. In contrast, the presently pending claims recite that the linker can be a streptavidin-biotin complex and that it may be used to link a therapeutic protein with the transport aid in a pH-dependent manner such that the therapeutic protein and transport aid remain operably linked at the neutral pH environment of the CSF but can become dissociated once taken up by cells into lysosomal compartments or other acidic intracellular organelles. The pH-dependent aspect of the claimed linker complex demonstrates the unexpected effect of the claimed invention, whereas Beliveau *et al.* teaches away from the present invention by indicating that the inclusion of the streptavidin-biotin linker is not critical.

The Office Action also rejected Claims 7, 16-17, 34, 44, 60 and 68 as being unpatentable over Elsberry *et al.* in view of Allen *et al.* and Beliveau *et al.*, and further in view of U.S. 6,015,572 (Lin *et al.*). Regarding Claims 7, 34 and 60, the Office Action alleged that Lin *et al.* teaches GDNF, FMRP and combinations thereof. However, insofar as the independent base

claims are patentable over the other references, as set forth above, these dependent claims are also nonobvious.

Regarding Claims 16-17, 44 and 68, the Office Action alleged that Lin *et al.* teaches that the therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation wherein integrity and activity of the protein formulation is achieved by adding at least one species operable for maintaining a desired pH to the therapeutic protein formulation. However, the present specification teaches at paragraph [0086] that acceptable levels of the solution pH for the therapeutic protein formulations of the invention are those that "generally maintain the integrity of the therapeutic protein/enzyme." Hence, the pH disclosure of Lin *et al.* is directed to maintaining integrity and activity of the species within the formulation prior to crossing the blood-brain barrier, whereas the pH-dependent feature of the claimed invention is directed to selective delivery and subsequence disassociation once the protein has crossed the blood-brain barrier. Hence, Lin *et al.* fails to teach the disassociation in an acidic environment once the composition crosses the blood-brain barrier, which is a feature that is clearly described in the pending claims.

Conclusion

In light of the foregoing, it is submitted that the application is now in condition for allowance. It is therefore respectfully requested that the rejections be withdrawn and the application passed to issue.

Respectfully submitted,
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